REMARKS/ARGUMENTS

Applicants acknowledge with appreciation the rejoining of Groups I and II for examination. Claims 1-19 and 23-25 are pending in the application. Claim 2 has been cancelled. Claims 1, 3, 17, 18, and 19 have been amended. Support for the amendments can be found, for example, in original claim 2 and on page 12, lines 15-29; page 13, line 14 through page 14, line 29; in working Example 1 on pages 22 *et seq.*, particularly page 23, line 9 through page 24, line 4 (for the limitation specifying the deposition of a Langmuir-Blodgett film on said sensor); and on page 16, line 26 through page 17, line 7 (for "optimal surface pressure"). No new matter has been added by way of amendment. Reexamination and reconsideration of the claims are respectfully requested.

The Rejections of Claims Under 35 U.S.C.§112, Second Paragraph, Should Be Withdrawn

The Office Action (August 6, 2004, page 2, #2) has rejected claims 1-19 as being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" due to the recitation of various terms and phrases.

Claim 1 was rejected because step (b) recited the phrase "preparing said peptide to be coupled to a sensor," and the Office Action stated that it was "not clear what steps are needed for preparing the peptides to couple to the sensor." Techniques are known in the art for attaching peptides to other moieties, and support is also provided in the specification, for example: on page 10, line 15 through page 11, line 15; on page 14, lines 6-12; in working Example 1 in the Experimental Section beginning on page 22; and in Example 2 in the Experimental Section beginning on page 30, line 13. Applicants believe that one of skill in the art, given the guidance provided by the specification, would understand and be able to perform the steps necessary to prepare the peptide to be coupled to the sensor. Nevertheless, in order to advance prosecution, claim 1 has been amended to omit step (b). Accordingly, the rejection of claim 1 and its dependent claims on this basis has been obviated by amendment and should be withdrawn.

Claim 1 was rejected because step (e) recited "quantifying the signal output," which was stated to lack antecedent basis (Office Action of August 6, 2004, page 2, #2). Step (e) of claim 1 has been amended to refer to "***a*** signal output" rather than "***the*** signal output" and therefore Applicants believe that the lack of antecedent basis has been addressed. Accordingly, the rejection of claim 1 and its dependent claims on this basis has been obviated by amendment and should be withdrawn.

Claim 3 was rejected because step (b) recited "an aqueous subphase," and the term "subphase" was stated to be unclear (Office Action of August 6, 2004, page 2, #2). Applicants respectfully submit that this terminology is standard in the area of Langmuir-Blodgett apparatuses and film formation and that one of skill in the art would readily understand the meaning of this term. Also, there is extensive support in the specification for this terminology throughout the specification and particularly on page 16, lines 1-8, which is as follows:

> 'Subphase' as used herein refers to an aqueous solution onto which the composition to be formed into a monolayer is spread. At least one bivalent and one monovalent cation must be present in the subphase. Suitable subphase include but are not limited to those described by Gains ('Insoluble monolayers at liquid-gas interface.' (1996) Interscience, New York). A typical subphase comprises: 55.0 mM KC1, 4.0 mM NaC1, 1.0 mM MgC12, 0.1 mM CaC12 and 2.0 mM MOPS buffer in deionized doubly distilled water, pH 7.4. The subphase is placed in the trough of the Langmuir-Blodgett apparatus prior to spreading the monolayer.

As is also discussed in the specification, the term "subphase" recognizes the notion that the composition is spread on the surface of the aqueous solution; *i.e.*, the air/liquid interface, giving rise to the notion of the aqueous solution as a "subphase." In addition to being below the air/liquid interface, the aqueous subphase will also be below the layer which is formed by spreading the desired composition onto the air/liquid interface. This process is described in detail in the specification; for example, in Example 2 beginning on page 30, particularly on page 33, lines 16-19, the formation of a monolayer is described in detail:

> The microscope slide is next immersed in the subphase so that the area of the slide covered by the antiserum [is] completely submersed. The slide is then withdrawn completely from the subphase solution.

In view of the above discussion, Applicants respectfully submit that the term "subphase" is not unclear and does not render the claim indefinite; accordingly, this rejection should be withdrawn.

Claim 3 was also rejected because step (d) recites the phrase, "a desired surface pressure," which was stated to be vague and indefinite (Office Action of August 6, 2004, page 3, continuation of #2). Applicants believe that the meaning of this phrase is made clear in the following passage of the specification (page 16, line 26 through page 17, line 7):

> Compression of a monolayer results in a transition from a gas phase to a liquid phase. Additional compression results in a transition from a liquid phase to a solid phase in which the molecules of the monolayer form a tightly packed, ordered structure. Further compression results in a collapse of the monolayer due to mechanical instability and a concomitant decrease in surface pressure. If the monolayer has more than one component, for example an antibody component, there may be a first collapse pressure at which the antibodies collapse and a second higher collapse pressure at which the rest of the monolayer collapses. Graphing of the surface pressure in response to movement of the compression barrier produces an isotherm that may be used to determine the optimal compression for a particular monolayer under a particular set of conditions. The **optimal surface pressure** is achieved just before a pressure is reached that results in the collapse of one or more monolayer components.
>
> After the **desired surface pressure** is achieved by compression of the monolayer, an LB film may be formed by passing a substrate through the monolayer one or more times.

(emphasis added) Applicants believe that the above passage makes clear to one of skill in the art that "desired surface pressure" has the same meaning as "optimal surface pressure." Nevertheless, in order to advance prosecution, claim 3, step (d) has been amended to recite the step of "compressing said monolayer to an **optimal** surface pressure." As shown in the passage above, the phrase "optimal surface pressure" is explicitly defined as being the surface pressure just before a pressure is reached that results in the collapse of one or more monolayer components. In view of this explicit definition, which will be understood by one of skill in the art, Applicants respectfully submit that the rejection of claim 3 on this basis has been obviated by amendment and should be withdrawn.

Claims 17 and 19 were rejected due to their recitation of "the prior round of screening," which was stated to lack antecedent basis (Office Action of August 6, 2004, page 3, continuation of #2). Both of these claims have been amended to refer to "**a** prior round of screening," which Applicants believe should address the rejection. Accordingly, the rejection of claims 17 and 19 on this basis has been obviated by amendment and should be withdrawn.

Claim 18 was rejected due to its recitation of "*in vivo* screening" and also due to its recitation of "sensor" (Office Action of August 6, 2004, page 3, continuation of #2). Applicants believe that both of these terms are sufficiently defined in the specification, as further discussed in detail below.

"*In vivo* screening" is known in the art and is discussed in the specification in several places, for example, on page 2, lines 1-5; page 7, lines 17-23 (incorporating by reference U.S. Pat. No. 5,622,699); in working Example 1 beginning on page 22 (see the data presented in Table 3 on page 29); and in references cited therein. The references cited on these pages explain in detail the procedures for *in vivo* screening. Generally, as described in great detail in these references, *in vivo* screening comprises injecting a particular protein (often expressed as a surface protein on an engineered bacteriophage) into an animal, followed by the sacrifice of the animal and the examination of its tissues. As will be clear to one of skill in the art, step (a) of claim 18 refers to *in vivo* screening, and the rest of the steps set forth in claim 18 refer to the preparation of a sensor device using a peptide of interest that was identified in step (a).

Sensors suitable for use in the invention are also discussed in the specification, for example, on page 11, line 19 through page 12, line 4. As stated in this passage in the specification:

> In some embodiments, a mass-sensitive sensor is used; alternatively, other sensors may be used so long as they are capable of detecting the binding of peptide of interest to ligand and providing signal output that changes in response to that binding. A direct correlation of binding and signal output is not required so long as the desired result is obtained. Thus, when binding occurs, different physical and electrochemical properties of the sensor may be changed: mass; free energy; electrical properties such as charge and conductance; optical properties such as fluorescence,

> luminescence, adsorption, scatter, and refraction. Accordingly, suitable sensors include electrochemical, calorimetric, and optical sensors. See, for example, Luppa *et al.* (2001) *Clinica Chimica Acta* 314: 1-26. One of skill in the art will appreciate that for different applications of the assays of the invention, sensors with different sensitivities and outputs may be used. Thus, for example, in some applications a preferred LSD will be capable of high-resolution quantitation of changes in binding, while for other applications an LSD need only detect the presence or absence of high-affinity binding.

In some embodiments, the sensor comprises a piezoelectric crystal which may be an acoustic wave sensor (see, *e.g.*, page 11, lines 16-19). Thus, as one of skill in the art is aware, there are a variety of sensors which are suitable for use in the compositions and methods of the invention. Applicants submit that because the term "sensor" is discussed extensively in the specification, one of skill in the art would agree that the term "sensor" is clear. Accordingly, this basis for the rejection of claim 18 should be withdrawn.

In light of the above amendments and discussion, Applicants respectfully request the withdrawal of the rejections of the claims for indefiniteness.

The Rejections of Claims Under 35 U.S.C.§102 Should Be Withdrawn

The Office Action (August 6, 2004, page 3, #4) has rejected claims 1, 8, 9, 14, 15, and 16 under 35 U.S.C. §102(b) as being anticipated by Hengerer *et al.* (1999) *Biosensors & Bioelectronics* 14: 139. The Hengerer reference is characterized as disclosing an immunosensing system based on a quartz crystal microbalance to detect target molecules in a sample. Applicants note that independent claim 1 (and therefore also claims 8, 9, 14, 15, and 16 which are dependent on or incorporate the limitations of claim 1) has been amended to specify that the sensor is prepared to be coupled to said peptide by depositing a Langmuir-Blodgett film on said sensor. In order for a reference to anticipate a claim, the reference must teach every element of the claim. (See MPEP §2131.) Here, the Hengerer reference does not teach the limitation of depositing a Langmuir-Blodgett film on the sensor and therefore it cannot anticipate the claimed invention. Accordingly, the rejection of claims under 35 U.S.C. §102(b) over the Hengerer reference has been obviated by amendment and should be withdrawn.

The Office Action (August 6, 2004, page 3, #5) has rejected claims 1 and 14 under 35 U.S.C. §102(b) as being anticipated by Suleiman *et al.* (1994) *Analyst* 119: 2279. The Suleiman reference is characterized as teaching an immunosensor to detect target molecules in a sample. Applicants note that independent claim 1 (and therefore also claim 14 which is dependent on claim 1) has been amended to specify that the sensor is prepared to be coupled to said peptide by depositing a Langmuir-Blodgett film on said sensor. In order for a reference to anticipate a claim, the reference must teach every element of the claim. (See MPEP §2131.) Here, the Suleiman reference does not teach the limitation of depositing a Langmuir-Blodgett film on the sensor and therefore it cannot anticipate the claimed invention. Accordingly, the rejection of claims under 35 U.S.C. §102(b) over the Suleiman reference has been obviated by amendment and should be withdrawn.

The Office Action (August 6, 2004, page 3, #6) has rejected claims 1-4, 14-15, and 23-24 under 35 U.S.C. §102(a) as being anticipated by Pathirana *et al.* (2000) *Biosensors & Bioelectronics* 15:135. Particularly, the Office Action (August 6, 2004, page 4, #6) states:

> With respect to claims 2-4, Pathirana et al. teach coating (e.g., preparing) phospholipids on a Langmuir-Blodgett film as a monolayer for peptide immobilization (See Section 2.6.1 Surface technique and Section 2.6.2.1 Phospholipid Monolayers). Furthermore, Pathirana et al. teach using 2% volatile organic solvent ethanol for deposition of the phospholipids. Supra. The monolayer was formed on the air-liquid interface by allowing the spreading solution to run down an inclined wettable planar surface that is partially submersed, e.g., 90-170 degrees, into the subphase. (See Figure 1 and Section 2.6.2.1) The flow rate down the plate was maintained at about 0.1 ml/min with a constant surface compressing pressure of 23 mN/m. (Section 2.6.2.1)

Applicants have submitted with this Amendment a Declaration of inventor Dr. Vitaly Vodyanoy under 37 CFR §1.132 which establishes that the Pathirana reference is not "by another" under the meaning of the statute. In accordance with MPEP §2132.01, the Declaration of Dr. Vitaly Vodyanoy establishes that the relevant disclosure in the cited reference was derived from the work of coinventors named on the present application. Particularly, Vitaly Vodyanoy and Suram T. Pathirana are both coauthors of the Pathirana reference and are also inventors of the claimed invention. As discussed in Dr. Vodyanoy's declaration, the work cited in the Office Action as

the basis for the rejection was performed either by Dr. Vodyanoy or by coinventor Suram T. Pathirana. Therefore, all of the subject matter in the Pathirana reference that has been asserted as the basis for the rejection of claims under 35 U.S.C. §102(a) is subject matter that originated with inventors of the present patent application. Accordingly, the Pathirana reference is not "by another" under 35 U.S.C. §102(a) and is not prior art against to the present patent application. In view of this discussion, Applicants respectfully submit that the rejection of claims under 35 U.S.C. §102(a) over the Pathirana reference should be withdrawn.

The Office Action (August 6, 2004, page 5, #7) has rejected claims 1, 8, and 9 under 35 U.S.C. §102(a) as being anticipated by Birkert *et al.* (2000) *Anal. Biochem.* 282: 200. The Birkert reference is characterized as teaching an immunoassay for detecting binding of a ligand on a Reflectometric Interference Spectroscopy Sensor. Applicants note that independent claim 1 (and therefore also claims 8 and 9 which are dependent on claim 1) has been amended to specify that the sensor is prepared to be coupled to said peptide by depositing a Langmuir-Blodgett film on said sensor. In order for a reference to anticipate a claim, the reference must teach every element of the claim. (See MPEP §2131.) Here, the Birkert reference does not teach the limitation of depositing a Langmuir-Blodgett film on the sensor and therefore it cannot anticipate the claimed invention. Accordingly, the rejection of claims under 35 U.S.C. §102(a) over the Birkert reference has been obviated by amendment and should be withdrawn.

In light of the above amendments and discussion, Applicants respectfully request the withdrawal of the rejections of the claims for anticipation.

The Rejections of Claims Under 35 U.S.C.§103 Should Be Withdrawn

The Office Action (August 6, 2004, page 6, #10) has rejected claim 25 under 35 U.S.C. §103(a) as being obvious over the Pathirana reference in view of the Birkert reference. As discussed above, the Pathirana reference is not prior art against the application because it is not "by another" under the meaning of 35 U.S.C. §102(a). Therefore, the Pathirana reference is not available as a reference against the claims under 35 U.S.C. §103. MPEP §2141.01. Accordingly, the rejection of claim 25 under 35 U.S.C. §103(a) over Pathirana in view of Birkert should be withdrawn.

The Office Action (August 6, 2004, page 6, #11) has rejected claims 6 and 7 under 35 U.S.C. §103(a) as being obvious over the Hengerer reference in view of Ebato *et al.* (1994) *Anal. Chem.* 66: 1683. As discussed above with regard to the rejection of claims under 35 U.S.C. §102(b) over the Hengerer reference, Applicants note that independent claim 1 (and therefore also claims 6 and 7 which are dependent on or incorporate the limitations of claim 1) has been amended to specify that the sensor is prepared to be coupled to said peptide by depositing a Langmuir-Blodgett film on said sensor. In order to establish a *prima facie* case of obviousness, the prior art references when combined must teach or suggest all of the claim limitations. MPEP §2142. Here, neither the Hengerer reference nor the Ebato reference teaches the limitation of depositing a Langmuir-Blodgett film on the sensor. Therefore, these references cannot render the claimed invention obvious. Accordingly, the rejection of claims under 35 U.S.C. §103(a) over the Hengerer reference and the Ebato references has been obviated by amendment and should be withdrawn.

The Office Action (August 6, 2004, page 7, #12) has rejected claims 5, 10-13, and 18-19 under 35 U.S.C. §103(a) as being obvious over the Pathirana reference in view of Samoylova *et al.* (1999) *Muscle & Nerve* 22: 460-466. As discussed above, the Pathirana reference is not prior art against the application because it is not "by another" under the meaning of 35 U.S.C. §102(a). Therefore, the Pathirana reference is not available as a reference against the claims under 35 U.S.C. §103. (See MPEP §2141.01.) Accordingly, the rejection of claim 25 under 35 U.S.C. §103(a) over Pathirana in view of Samoylova should be withdrawn.

In light of the above amendments and discussion, Applicants respectfully request the withdrawal of the rejections of the claims for obviousness over the cited references.

Consideration Of Previously Submitted Information Disclosure Statement

It is noted that initialed copies of the PTO Forms 1449 that were submitted with Applicants' Information Disclosure Statements filed June 26, 2002 and January 31, 2003 have not been returned to Applicants' representative with the Office Action. Accordingly, it is

requested that an initialed copy of these Forms 1449 be forwarded to the undersigned with the next communication from the PTO. In order to facilitate review of the references by the Examiner, copies of the Information Disclosure Statements and the Forms 1449 are attached hereto. Copies of the cited references were provided at the time of filing the original Information Disclosure Statement, and, therefore, no additional copies of the references are submitted herewith. Applicants will be pleased to provide additional copies of the references upon the Examiner's request if it proves difficult to locate the original references.

CONCLUSION

In view of the above amendments and remarks, Applicants submit that the rejections of the claims under 35 U.S.C. §§112, second paragraph, 102(b), and 103(a) are overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required

therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Lynda-Jo Pixley